Current and Future Treatment Trends in Diabetic Macular Edema

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Diabetic macular edema (DME) is the most common cause of visual loss in patients with nonproliferative diabetic retinopathy (DR) and is a frequent cause in patients with proliferative diabetic retinopathy (PVR). The pathogenesis of DME is multifactoral and is influenced by risk factors including hypertension, proteinuria, the duration of diabetes, the degree of glycemic control, and specific systemic medications. Ultimately, however, DME results from upregulation of vascular permeability factors, which break down the blood-retina barrier, enabling fluid to leak from abnormal retinal capillaries and microaneurysms.

Treatment goals in patients with DME include resolving the edema, improving visual acuity, preventing recurrence, minimizing side effects and number of treatments, and controlling cost. The first line of treatment in all patients with DME is medical control. Weight loss and exercise should be advocated, and hypertension and glycemic control should be vigilantly regulated. When the edema meets criteria consistent with clinically significant macular edema (as defined in the Early Treatment of Diabetic Retinopathy Study [ETDRS]), further intervention is warranted. The ETDRS established focal or grid laser photocoagulation as the gold standard. At 3 years, 12% of patients treated with laser lost ≥15 letters compared to 24% of untreated controls.[1] The ETDRS demonstrated that laser photocoagulation could significantly reduce vision loss from diabetic macular edema.

While a reduction in visual loss is certainly important, patients with declining vision are eager to improve their vision. In ETDRS, only 17% gained ≥3 lines of visual acuity after undergoing focal/grid laser for DME.[2]The majority of patients neither lost nor gained visual acuity from baseline. With this in mind, many alternative therapies have been sought not only to further minimize visual loss from DME, but also to improve vision.

CORTICOSTEROIDS

Corticosteroids diminish inflammation, downregulate cytokines including vascular endothelial growth factor (VEGF), and stabilize the blood-retina barrier. As a result, they have received a great deal of attention in the management of diabetic macular edema. For treatment of ocular diseases, corticosteroids can be delivered via multiple routes: via intravitreal injection, sub-Tenon's injection, or systemically. Given their extensive side effect profile, local rather than systemic administration is preferable whenever feasible and safe.

In cases of DME, intravitreal administration has the major benefit of delivering drug directly to the site of pathology in relatively large doses. With this benefit come several potential drawbacks. Patients who receive intravitreal corticosteroid administration are at increased risk for cataracts, glaucoma, and endophthalmitis, among other side effects. Despite these potential risks, several authors have found intravitreal triamcinolone acetonide (IVTA) to be effective, both in eyes with treatment naive macular edema and in eyes with edema refractory to previous laser treatment. Martidis et al[3] demonstrated improvement in visual acuity at 1, 3, and 6 months after IVTA. In addition, central macular thickness on optical coherence tomography (OCT) improved at all time points compared with baseline.[3] Similarly, Batioglu et al[4] found central macular thicknesses on OCT improved at all time points up to 24 months after IVTA. In Batioglu's cohort, visual acuity improved at 1- and 3- month follow-up but was not statistically different beyond 6 months. Additionally, 39% of patients required reinjection, and the authors found that injection-related complications, such as cataracts and glaucoma, increased with extended follow-up. A large multicenter clinical trial conducted by the Diabetic Retinopathy Clinical Research Network (DRCR.net) has shown that, in a comparison of the efficacy and safety of 1 mg and 4 mg of preservative free triamcinolone vs focal/grid photocoagula-

tion, laser was more effective and had fewer side effects.[5]

In clinical practice, IVTA has a duration of action of approximately 3 to 6 months. In patients with severe or refractory disease, retreatment is often necessary. Batioglu et al found that nearly 2 out of 5 patients required retreatment over a 24-month period. Each retreatment exposes patients to additional endophthalmitis risk and makes cataract formation more likely (in phakic patients). These factors have driven pharmaceutical companies to develop longer-acting corticosteroids that can be delivered intravitreally. Two corticosteroids that are currently in phase 3 trials are DDS-Posurdex (Dexamethasone Posterior Segment Drug Delivery System, Allergan, Inc., Irvine, CA) which lasts for 6 months, and the Medidur (fluocinolone acetonide, Alimera Sciences, Alpharetta, GA) which may last up to 3 years. If these medications obtain US Food and Drug Administration (FDA) approval, the benefits of a long-term single injection of corticosteroid will need to be weighed carefully against the side effects.

Given the inherent risks of injecting corticosteroids intravitreally, some clinicians advocate sub-Tenon's administration. The goal is to deliver a bolus close enough to the eye that absorption can occur, while still limiting systemic side effects. Even with subtenon's injection, however, glaucoma and cataract can occur. Barring a needle penetration, however, endophthalmitis does not occur after sub-Tenon's administration, and all ocular side effects are less common than with intravitreal injection.

Early evidence suggested that sub-Tenon's corticosteroids were effective. Toda et al[6] found that injecting 20 mg of sub-Tenon's triamcinolone reduced mean central macular thickness at 1 and 3 months. A prospective multicenter randomized clinical trial conducted by the DRCR.net, however, found no statistical difference between focal photocoagulation alone and sub-Tenon's triamcinolone alone or combined with focal photocoagulation.[7] As a result, they concluded that sub-Tenon's triamcinolone was unlikely to offer a substantial benefit in cases of DME with good visual acuity. In addition to its questionable efficacy, there is preliminary evidence that sub-Tenon's dexamethasone may raise systemic glucose levels similar to levels after intravenous pulse methylprednisolone.[8] In brittle diabetics this could be particularly troublesome and may factor into the treatment decision paradigm.

ANTI-VEGF AGENTS

Vascular endothelial growth factor is an important modulator of blood vessel growth and permeability. High levels of ocular VEGF have been demonstrated in patients with DME,[9] making VEGF an attractive target when treating DME. There are currently many agents that target various VEGF isomers or precursors. The commercially available agents include bevacizumab (Avastin, Genentech), ranibizumab (Lucentis, Genentech), and pegaptanib sodium (Macugen, OSI/Eyetech), while products in the pipeline include VEGF Trap (VEGF-Trap Eye, Regeneron) and small interfering RNA (siRNA, Merck), among others.

Bevacizumab is FDA-approved for the treatment of colon cancer by intravenous infusion. It is a humanized monoclonal antibody that binds and deactivates all VEGF-A isoforms. Since this drug gained acceptance as an off-label treatment of neovascular age-related macular degeneration by intravitreal administration, attention has recently centered on other disease states where treatment with bevacizumab may be beneficial. Arevalo et al[10] retrospectively evaluated intravitreal bevacizumab as a primary treatment for DME. At 6 months follow-up, mean central macular thickness on OCT improved compared to baseline. In addition, 55% of patients had a two or more line gain in ETDRS best corrected visual acuity (BCVA) gain, 41% of patients had stable BCVA, and 4% of patients had a two or more line decrease of BCVA. Other studies have also looked at intravitreal bevacizumab as a treatment of DME refractory to previous laser photocoagulation.[11,12] These studies also showed improved central macular thickness and improved visual acuity at 3 and 6 months follow-up.

As with IVTA, intravitreal bevacizumab frequently requires multiple injections over time. Arevelo et al[10] found that 20.5% of patients required a second injection and 7.7% required a third injection. Although endophthalmitis is also a risk after injection with bevacizumab, cataract formation and glaucoma seem to be less of an issue than with IVTA. Paccola et al[13] compared the efficacy of a single dose of IVTA vs bevacizumab in patients with refractory DME and found that IVTA improved central macular thickness more than bevacizmab at 4, 8, 12, and 24 weeks.

Other anti-VEGF agents are currently being studied in randomized multicenter clinical trials. Pegaptanib inhibits $VEGF_{165}$ the most abundant isoform of the VEGF-A family. Ranibizumab is a humanized antibody fragment that blocks all VEGF-A isoforms and their active degradation products. In a phase 2 clinical trial, patients with DME who received pegaptanib were more likely to improve visual acuity and reduce central macular thickness and were less likely to require additional laser treatment.[14] Phase 3 trials are ongoing with both pegaptanib and ranibizumab as a treatment for DME. As other inhibitors of VEGF reach the market, they too will likely be evaluated for the treatment of DME.

PARS PLANA VITRECTOMY

The role of the vitreous as a possible causative or contributory factor in DME was first recognized by Nasrallah

et al[15] in 1988, when they retrospectively demonstrated lower rates of posterior vitreous detachment in patients with macular edema compared with controls. Lewis et al[16] later performed pars plana vitrectomy (PPV) with separation of the posterior hyaloid in 10 patients with DME and traction associated with a "thickened and taut premacular posterior hyaloid." Visual acuity improved postoperatively in nine of the 10 eyes.

Many recent studies have focused on the possible benefits of PPV for the treatment of DME.[17-50] It appears that in select cases PPV may improve diabetic macular edema and improve visual acuity and that the effects may be long lasting. Yamamoto et al[51] reviewed 73 cases of PPV for DME and found that patients improved BCVA by 12 months and maintained these improvements for at least 24 months.

Although it is appears that PPV offers benefits in certain patients, controversy exists regarding the exact surgical technique and the degree of benefit. Current disagreement centers upon the necessity of peeling the internal limiting membrane (ILM). Numerous retrospective studies have shown visual improvement with PPV and removal of the posterior hyaloid alone (ie, without ILM peeling). Similarly, PPV with ILM peeling has been shown to be effective. Yanyali et al[52] found that PPV with ILM peeling improved visual acuity and reduced DME in a retrospective review of 27 cases. Similarly, Rosenblatt et al[53] found that PPV with ILM peeling decreased retinal thickness and improved visual acuity in cases of refractory DME without a taut posterior hyaloid. Stefaniotou et al[54] sought to answer whether or not PPV with ILM peeling was superior to PPV with removal of the posterior hyaloid alone. In their retrospective review of 73 eyes, 69% of eyes with ILM peel had complete resolution of DME vs 44% without ILM peeling. They concluded that PPV with ILM peeling yielded better results. Kumagai et al,[47] on the other hand, found no difference in DME absorption rate whether or not ILM was peeled.

Expert opinions also diverge when considering combination treatment. Because of the encouraging results of PPV in the treatment of DME, many surgeons are using PPV as one arm of a multi-treatment approach—combining vitrectomy with either laser or intravitreal pharmacotherapy. Kang et al[55] combined PPV with IVTA and macular laser photocoagulation and concluded that this combination may facilitate early visual recovery and improve long-term outcomes in patients resistant to conventional treatment.

While there may be benefits to PPV, surgical remedy is not without its drawbacks. Patients who undergo PPV are at increased risk for cataracts, endophthalmitis, rhegmatogenous retinal detachment, and other unfavorable outcomes. Patients who undergo additional ILM peeling may also be more likely to experience iatrogenic macular trauma or, rarely, phototoxicity. Decision to undergo surgical remedy should, therefore, only be undertaken after careful consideration of the risks, benefits, and alternatives.

RUBOXISTAURIN MESYLATE

Protein kinase C (PKC) is known to play an important role in the development of diabetic microvascular complications of the eye and elsewhere, and it likely has a role in the development of DME. Ruboxistaurin mesylate (Eli Lilly) is an orally administered PKC-beta inhibitor. As such, it may hold promise in the treatment or prevention of DME.[56] Several reports suggest that ruboxistaurin mesylate may prevent DME. One early study showed that ruboxistaurin mesylate at a dose of 32 mg/day resulted in less visual loss than did placebo, particularly in patients with DME.[57] In a second study, ruboxistaurin mesylate reduced the need for laser photocoagulation to treat macular edema. In addition, it decreased the frequency with which edema progressed to within 100 µm of the foveal vascular zone.[58] Most recently, the PKC-Diabetic Macular Edema study group reported 30-month results on the safety and efficacy of ruboxistaurin mesylate: ruboxistaurin mesylate did not delay the need for focal/grid photocoagulation, but it may delay the progression to sight threatening DME.[59]

Although ruboxistaurin has been well tolerated with limited side effects, the FDA recently asked for additional data prior to clinical approval. This would require the manufacturer to run an additional 3-year, phase 3 trial to provide additional efficacy data.

GLITAZONES

The glitazones are a class of oral medications used to treat diabetes. They function by improving hepatic and skeletal muscle insulin sensitivity and concomitantly decreasing hepatic output. The first available glitazone—troglitazone—was removed from the market by the FDA in 2001 due to safety concerns. Two glitazones are currently commercially available, rosiglitazone (Avandia, GlaxoSmithKline), and pioglitazone (Actos, Takeda). In 2005, Coluciello described DME-related vision loss from rosiglitazone.[60] In 2006, Ryan et al[61] described a series of 30 patients who used pioglitazone or rosiglitazone and had both lower extremity edema as well as macular edema. The authors concluded that in certain individuals glitazones may cause both fluid retention and macular edema and that cessation of glitazones results in rapid resolution of both.

CONCLUSION

Diabetic macular edema is a frequent cause of vision loss, especially in patients with long-standing diabetes. Treatment goals in these patients include resolving the edema, improving visual acuity, preventing recurrence, minimizing side effects and number of treatments, and controlling cost.

Although hypertension and blood sugar control are critical to achieve these goals, pharmacotherapy and surgical intervention will continue to play a future role in these patients both in the prevention and the treatment of disease. ■

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